REMARKS

Claims 7-10 are pending in this application. Claims 7 and 9 stand rejected under 35 USC 102(b) over Doiron; claim 8 is rejected under 35 USC 103(a) over Doiron in view of Kaas; and claim 10 is rejected under 35 USC 112, second paragraph. Claim 10 have been amended in view of the Examiner's comments on the nature of ultrasound, thereby obviating the rejection under 35 USC 112, second paragraph. Each of the remaining rejections is respectfully traversed. No new matter has been added by these amendments.

Claim 10 is rejected under 35 USC 112, second paragraph, as the Examiner finds that ultrasound does not fall within the scope of the term "electromagnetic radiation". Although applicants do not agree that this is necessarily the case, claim 10 has been amended to recite that the topical agent is exposed to a source of ultrasound. This feature of the invention is thoroughly described in the specification, thus no new matter is added. The rejection should, therefore, be withdrawn upon reconsideration.

Claims 7 and 9 are rejected under 35 USC 102(b) over Doiron. Doiron, however, does not teach, disclose or suggest each and every element and limitation of claim 7. For this reason, the rejection is respectfully traversed.

Nowhere does Doiron teach "selecting at least one of a photoactive agent and a photosensitizing agent, the agent having an electromagnetic radiation absorption characteristic enabling the agent to absorb at least a first wavelength of electromagnetic radiation from an electromagnetic radiation source." Nowhere does Doiron teach the selection of a photosensitizing agent or photoactive agent. This precludes the reference from teaching that the agent may be selected to absorb a particular wavelength of electromagnetic radiation.

The Examiner's misapprehension of the reference appears to be due to Doiron's mischaracterization of a reference cited in the background of the invention. Therein, Doiron states, "in the treatment of psoriasis or other hyperproliferative diseases of the skin, an array of discrete light sources may be employed to provide the power densities required to effect the therapy during the office visit. Such an array has been described, for example, by Jori et al. (*Porphyrins in Tumor Therapy*, Penum Press, N.Y., 301-308 (1984)." Col. 3, lines 37-48. Note, as well, that the Examiner has cited to this portion of the reference in support of the rejection.

Applicant has obtained a copy of the Jori reference (copy attached) and notes that nowhere does the Jori reference teach an array of LED's for treating psoriasis or similar skin disorders. Jori solely addresses the use of a high-power LED array for treating tumors using porphyrin compounds. Nowhere does Jori teach, disclose, or suggest the use of photoactive agents couple with radiation from an LED array for treating psoriasis. Moreoever, the Doiron reference itself is completely silent with respect to the use of photoactive or photosensitizing agents for treating psoriasis. This makes it impossible for Doiron to teach "applying the agent to at least a portion of the mammalian skin affected by psoriasis" as recited in claim 7.

For these reasons, neither Doiron, Jori or any combination of these reference taken alone or together as a whole teaches, discloses or suggests every feature and limitation of claim 7. The rejection of claim 7 and claims depending therefrom should, therefore, be withdrawn upon reconsideration.

Although the rejection of claim 8 under 35 USC 103(a) over Doiron in view of Kaas is now moot, applicant offers the following remarks with regard to the teaching of Kaas. The Examiner cites to col. 1 line 64 to col. 2, line 2 to suggest that Kaas teaches an energy fluence of 5.4 mJ/cm^2 for use in a system to treat psoriasis. This assertion is misleading – Kaas teaches an

energy fluence of 5.4 mJ/cm^2 to kill bacteria in the water flowing through a UV sensor system. Under no interpretation can Kaas be read to suggest an energy fluence delivered to subject of from 1 J/cm^2 to 10 J/cm^2 for use with a system for treating psoriasis employing photoactive or photosensitive agents. One of ordinary skill in the art, when reading Kaas, would have no motivation whatsoever to modify the energy fluence taught therein for sterilizing water, to arrive at the energy fluence of claim 7. The rejection of claim 8 under 35 USC 103(a) should, therefore, be withdrawn for this reason. As previously remarked, however, it is believed that the rejection is already moot in view of the earlier remarks with regard to the failure of Doiron to anticipate claim 7.

For these reasons, all claims are now in condition for allowance and a notice thereof is earnestly solicited.

In the event that the transmittal letter is separated from this document and the Patent and Trademark Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952**, referencing Docket No. **595982000211**.

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Respectfully submitted,

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A MULTI-LED SOURCE FOR PHOTORADIATION THERAPY

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INTRODUCTION

Light sources emitting at the long wavelength wing of the absorption spectrum of Hematoporphyrin (Hp), between 610 and 640 nm, are currently used in photoradiation therapy (PRT) in order to maximize penetration of light into the tumor mass. Optical output powers of several watts are necessary to ensure the suitable irradiance ($30\div100$ mW/cm^2) at the tumor surface. Filtered high-power Xenon or halogen lamps, and ion-laser-pumped dye lasers tuned at $\lambda_p \approx 630$ nm are the most common sources used so far. The overall electrical-to-optical conversion efficiency of these sources is quite small, typically 0.05% (0.2 for halogen lamps). Flash-lamp-pumped dye lasers are now commercially available at average output power of $10\div20$ W; the efficiency is $\sim 0.8\%$ in the red [1]. Their use for photodynamic therapy is under investigation [2]. Gold vapor lasers emitting $1\div6$ W at 628 nm with 0.2% efficiency represent another interesting new source for PRT of tumors [3].

A different class of light sources that could find application in the PRT of tumors is represented by Light Emitting Diodes (LEDs). These miniaturized solid-state lamps have been used almost exclusively as very low power indicators and displays untill recently; now the application in several growing fields (such as optical communications) has led to the development of high-efficiency, high-intensity LEDs. Red light emitting diodes are today commercially available at output powers of several milliwatts with an efficiency of $\sim 5\%$, and at low cost. As the emitted wavelengths range from

) to 680 nm a suitably shaped multi-LED system could provide the ecessary power density for the PRT of superficial tumors. The de-lopment of tightly-packed arrays of incoherent or coherent high-fficiency LEDs may lead to more compact sources for PRT, and, in rticular, to efficient optical fiber systems for endoscopic treat-nts.

In this paper the possibility of utilizing a multi-LED system light source to promote porphyrin-sensitized photoprocesses has en tested by following the Hp-sensitized photooxidation of the dnoacid L-tryptophan (Trp) either free or bound with human serum bumin (HSA), as well as the Hp-sensitised photokilling of HeLa ells. Both these systems have been previously investigated by us-g conventional light sources [4,5].

ATERIALS AND METHODS

The H-500 Hi-super bright red LED (GaAlAs) made by Stanley ectric Co, Ltd (Japan) has been chosen for the experiment. Nom-al values of output intensity, peak wavelength and spectral band-idth at I_F = 20 mA forward current (f.c.) and room temperature are = 500 mcd; λ_0 = 660 nm; $\Delta\lambda$ = 40 nm, respectively. All these pa-meters are strongly temperature dependent. A decrease of the op-rating temperature produces a blue-shift of the peak wavelength, nd a narrowing of the output spectrum; the total light intensity ncreases by several orders of magnitude when the diode is operated

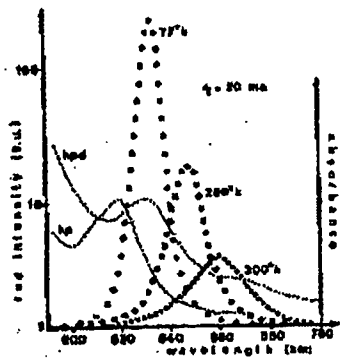

Fig. 1.

at 77°K. Fig. 1 shows the emission spectra (at 20 mA f.c.) of the H-500 LED at several temperatures, together with the absorption spectra of Hp and Hp derivative (HpD). As it can be seen, at room temperature the absorption by Hp is expected to be low due to the 30 nm shift between LED emission and Hp absorption maxima[6]. By reducing the LED temperature, the emission maximum can be brought into coincidence with the 630 nm peak of HpD: the narrower spectrum and the much higher intensity should now greatly enhance the efficiency of the LED to excite HpD molecules.

In the experiment the H-500 LED has been operated at room temperature and at 50 mA f.c.: output powers greater than 3 mW has been measured in these conditions. The LED collimating capsule provides a half-intensity full-divergence of 45°, i.e. half power of the LED can be collected on 1 cm^2 area target placed at 13.5 mm from the capsule. Thirtythree LEDs have been inserted into closely-packed, radially oriented holes in a metallic hemisphere with 15 mm inner diameter. The light intensity distribution over the central 1 cm^2 spot in the equatorial plane was sufficiently uniform with a power density of ~ 27 mW/cm^2 (at 50 mA f.c.).

RESULTS AND DISCUSSION

Hematoporphyrin-sensitized photooxidation of tryptophan and the tryptophyl residue of human serum albumin

When 0.7 ml of a 0.1 mM Trp solution in 0.05 M phosphate buffer at pH = 7.4 was irradiated in the presence of 100 μM Hp at ca. 20°C, the aminoacid underwent photooxidative modification according to first-order kinetics (Fig. 2.a,b). Such a behaviour is typical of porphyrin-promoted photodynamic processes [6]. The rate constant of the photoprocess was $1.3\ 10^{-4}\ s^{-1}$, i.e. one order of magnitude lower than that observed for the same system exposed to a He-Ne laser emitting ca. 25 mW/cm^2 at 632.8 nm[7]. The rate constant almost doubled (Fig. 2.b) when HSA-bound Hp was used as a photosensitizer for the modification of the unique Trp residue present in HSA. Under our experimental conditions, Hp yields a 1:1 ground state complex with HSA, the porphyrin binding site being at 1.7 nm from the indole side chain of the Trp residue[8]. The enhancement of the rate constant for photoprocesses promoted by protein-bound porphyrins has been previously observed[9] and ascribed to a greater triplet quantum yield for bound Hp as compared with free Hp and/or a shift in the overall photooxidation mechanism from a type II ($^1O_2$-involving) pathway to a type I (radical-involving) pathway.

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[a] At the time of the experiment the Hewlett-Packard LED HP 3750 emitting 160 mcd at 635 nm was not available. Its better matching of Hp absorption should compensate for the lower emission power.

Fig. 3.

-Arrays

Straightforward hybrid-circuit fabrication techniques should mit the assembly of single LED chips into tightly-packed arrays able of producing the irradiance needed for PRT, as already posed by Epstein et al. [11]. Integrated optical systems could n provide the suitable radiation pattern or efficient coupling optical fiber delivery systems. Fig. 3 shows a picture of a 2 array of four IR LEDs already available commercially.

de Lasers and Diode Laser Arrays

A number of single-emitter conventional semiconductor diode ers emit output powers in excess of 50 mW cw from a single facet the near IR [12]. For red diode lasers begin to be produced at er power (10-20 mW). Future development of high power diode ers at λ = 630 nm should permit very compact and efficient multi- ment sources for PRT.

Recently, cw operation of multiemitter (40) phase-locked arrays IR diode lasers has also been demonstrated at output power levels greater as 2.5 W [12]. Because the emission is coherent, the laser ht can be focused into a single diffraction-limited spot. When dlar powers will be available in the useful porphyrin absorption ge, important progresses will be registered in the phototechnol- of tumor therapy.

CONCLUSIONS

In this paper evidence has been presented that red light emitting diodes (LEDs) can be used to kill porphyrin-sensitized tumor cells. Multi-LED systems can provide the power density needed for therapy of superficial tumors. Operation of multi-LED (N-500) arrays at 77°K is expected to produce much higher power densities and to allow direct LED coupling to optical fibers for the treatment of internal tumors with large bore endoscopes. The application to PRT of future developments of incoherent LED-arrays, diode lasers, and diode laser arrays has also been discussed.

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